REMARKS

Claims 1, 5, and 7-8 are currently pending in this application. New claims 9-12 are added. Support for new claims 9 and 11 can be found, for example, in original claims 1 and 5, and in paragraphs [0012] and [0079] of the specification. Support for new claims 10 and 12 can be found, for example, in original claim 6 and paragraph [0079] of the specification. No new matter has been added.

Applicants respectfully submit that all of the pending claims are allowable for at least the following reasons.

I. The Rejection Under 35 U.S.C. § 112 Should be Withdrawn

Claims 1, 5, and 7-8 stand rejected under 35 U.S.C. § 112 as allegedly not enabled. *See* Office Action, page 3. The Examiner points out that the specification is enabled with respect to "methods of reducing elevated levels of PDE IV, or treating a mammal suffering from **inflammatory respiratory conditions, specifically asthma and COPD**, comprising administering an effective amount of a compound of formula (I) to said mammal…." *Id.* (emphasis in original).

A. Claims 1, 7 and 9-12

Applicants point out that pending claim 1 recites a method of reducing elevated levels of PDE IV in a mammal with a compound of formula (I). Pending claim 7 recites a method of reducing elevated levels of PDE IV in a mammal with a compound encompassed by formula (I). Therefore, according to the Office Action as quoted above, claims 1 and 7 are enabled by the specification. *Id.*

New claims 9-12 recite methods of treating an inflammatory respiratory condition, or asthma, with a compound of formula (I). These claims are enabled by the specification, as the Office Action points out at page 3, as quoted above.

For these reasons, Applicants respectfully request that the rejection of claims 1, 7 and 9-12 be withdrawn.

B. Claims 5 and 8

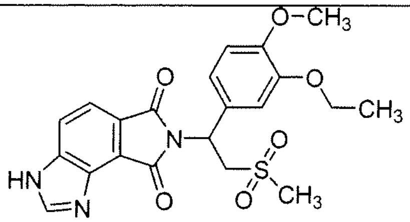
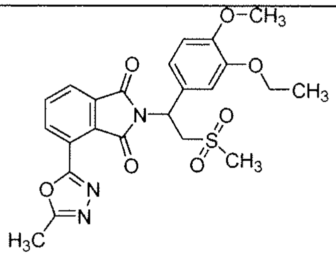
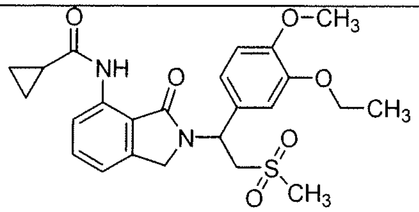
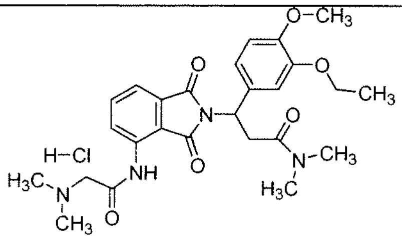
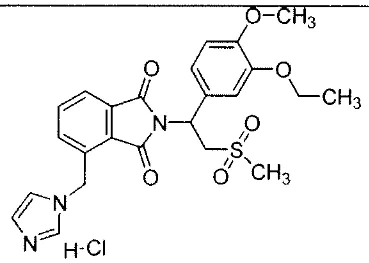
The Office Action alleges that the instant specification does not provide enablement for "other inflammatory or autoimmune diseases" outside of inflammatory respiratory conditions such as asthma and COPD. *See* Office Action, page 3. Applicants respectfully disagree, and point out that only claims 5 and 8 recite the treatment of "other inflammatory or autoimmune diseases" as recited by the Office Action.

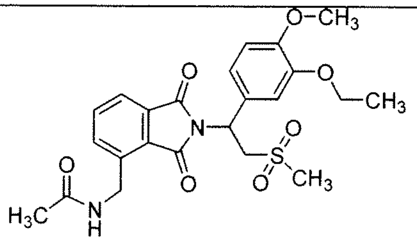
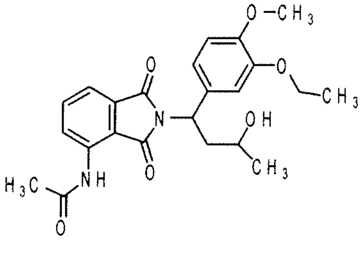
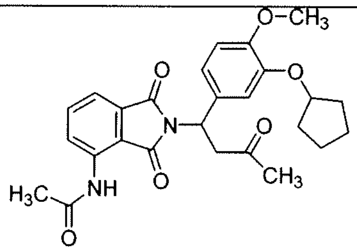
The Patent Office bears the burden of establishing a reasonable basis to question the enablement provided for a claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). Specifically, the Office must demonstrate that one ordinary skill in the art could not make or use the invention based on disclosure of the application in view of information available in the art without undue experimentation. *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). Here, the Office Action alleges that it would require undue experimentation to practice the full scope of the instant claims. *See* Office Action, pages 3, 13 and 16.

Applicants first point out that the disclosure of the "specification…must be taken as being in compliance with the enablement requirement…unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." Manual of Patent Examining Procedure ("MPEP") § 2164.04) (emphasis added). And, importantly, "not everything necessary to practice the invention need be disclosed. All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art." *Id.* at § 2164.08 (emphasis added).

Instant claims 5 and 8 are enabled by the specification because the specification teaches that compounds of the invention inhibit PDE IV, and that an inflammatory or autoimmune disease can be treated using these compounds. (Specification, page 24, lines 10-15). Methods of preparing the compounds are described in detail on pages 13-17 of the specification, as well as in the Examples section of this application. Dosages and routes of administration are described, for example, on pages 23-24 of the specification. All that is required for those of ordinary skill in the art to practice the claimed invention is to administer the specified amount of the specified compound using the specified routes of administration.

Furthermore, Applicants have provided *in vitro* data showing the efficacy of exemplary compounds in inhibiting PDE IV. (*See*, *e.g.*, Applicants' responses dated January 19, 2006 and September 27, 2005). The data provided are reproduced below:

Example #	Structure	PDE 4 IC$_{50}$ (μM)
3		0.356
15		0.658
55		0.278
61		0.287
65		0.095

66		0.105
71		0.543
76		0.198

The above data are further evidence that the compounds recited by the pending claims are indeed effective in inhibiting PDE IV. Therefore, considering all of the above, there is no reason to doubt that the specification provides sufficient guidance to allow those of ordinary skill in the art to make and use the claimed invention to the full scope recited in claims 5 and 8. *See* MPEP § 2164.04.

Despite the above, the Office Action alleges that the presumption of enablement of the instant claims is rebutted by evidence that *in vitro* and *in vivo* studies of PDE IV inhibitors are not always predictive of clinical results. *See* Office Action, pages 7-10. The Office Action cites the following three references in alleged support of this contention: Bielekova *et al.*, *J. Immunol.*, 2000, 164:1117-1124; Burnouf *et al.*, *Current Pharm. Design*, 2002, 8(14): 1255-1296; and Dastidar *et al.*, *Current Opin. Investig. Drugs*, 2007, 8(5): 364-372. *See* Office Action, pages 5-7.

Regarding Bielekova, the Office Action alleges that the reference teaches that "the simple extrapolation of therapeutic efficacy from animal models to human disorders is not easily feasible." *See* Office Action, page 6. While it is true that Bielekova at one point states that extrapolation from human to animal models is not always easy, the reference as a whole teaches that PDE inhibitors, including inhibitors of PDE IV, are promising as therapeutic targets for autoimmune diseases and disorders. *See* Bielekova, pages 1117 and 1123. Indeed, Bielekova concludes in the abstract that the findings discussed therein "broaden the understanding of the immunomodulatory actions of PDE inhibitors and underscore their promising drug profile for the treatment of autoimmune disorders." *Id.* at page 1117. Thus, contrary to the Office Action's conclusion, Bielekova indeed supports the enablement of the instant claims with respect to the use of PDE IV inhibitors for the treatment of autoimmune (*i.e.*, immunoregulatory) diseases and disorders.

Burnouf is a review article published about two years after the effective filing date of the instant application. It teaches that PDE IV inhibitors have shown potential for clinical use in the treatment of inflammatory and immunoregulatory diseases and disorders, including rheumatoid arthritis, atopic dermatitis, multiple sclerosis, Crohn's disease, colitis, acute lung injury, inflammatory pain, lymphoid malignancies, hypertension, osteopenia, erectile dysfunction, anxiety, diabetes, and HIV infection. *See* Burnouf, page 1258. Burnouf teaches that there was active development of PDE4 inhibitors for the treatment of a variety of inflammatory and immunoregulatory disease at the time of the invention. *Id.* Thus, Burnouf provides further evidence in support of the enablement of the instant claims.

The Office Action points to the abstract and page 1258 of Burnouf, to allege that "the clinical use of PDE4 prototype inhibitor drugs have been limited due to the side effects that occur at therapeutic plasma levels." *See* Office Action, pages 6-7. However, the passage cited by the Office Action relates only to rolipram, one clinically efficacious PDE inhibitor that has demonstrated mild side effects such as nausea and vomiting in some cases at doses over 15 mg daily. *See* Horowski *et al.*, *Curr. Ther. Res.*, 1985, 38(1): 23-25 (cited in Burnouf at page 1258 and provided in herewith in a supplemental Information Disclosure Statement). Rolipram was found to be free of other more serious side effects such as pulse rate, blood pressure, respiratory rate and motor side effects after repeated administration. *Id.* at page 25. Thus, contrary to the Office Action's assertion, PDE IV drugs have been shown to be efficacious and safe in human clinical trials. The mere fact that one such drug, rolipram, demonstrated mild side effects at an elevated dose does not change the fact that the drug is an example of the state of the art at the time of the invention, *i.e.,* that a PDE IV inhibitor demonstrated desired therapeutic effect in humans consistent with prior *in vivo* results in rats. *Id.; see also* Zeller *et al., Pharmacopsychiatry*, 1984, 17: 188-190 (cited in Burnouf at page 1258 and provided in herewith in a supplemental Information Disclosure Statement). In other words, Burnouf and the references cited therein support the enablement of the instant claims as evidence of a PDE IV inhibitor's *in vivo* effect being predictive of results in human trials. Indeed, the most recent rolipram clinical study cited in Burnouf concludes that "the predictions from animal studies…could be substantiated." *See* Hebenstreit *et al., Pharmacopsychiatry*, 1989, 22: 159 (cited in Burnouf at page 1258 and provided in herewith in a supplemental Information Disclosure Statement). Therefore, contrary to the allegations of the Office Action, Burnouf supports the enablement of the instant claims by teaching that PDE IV inhibitors have shown the potential for clinical use in the treatment of a number of inflammatory and immunoregulatory diseases and disorders, including the clinical results for rolipram as discussed above.

The Office Action also relies in part on Dastidar to allege that the instant claims lack enablement because the translation of preclinical success to clinical trials is not predictable. *See* Office Action, pages 7-8. Dastidar teaches that PDE IV inhibitors have therapeutic potential in the treatment of various inflammatory disease such as asthma, COPD, psoriasis, rheumatoid arthritis, and inflammatory bowel diseases, *e.g.*, Crohn's disease and ulcerative colitis. *See, e.g.*, Abstract. Dastidar further teaches that two PDE IV inhibitors, cilomilast and roflumilast, have successfully advanced to phase III clinical trials in humans with asthma with "encouraging data." *Id.* at 365-366. While Dastidar does mention that cilomilast and roflumilast have yet to receive regulatory approval due to their low therapeutic ratio, that fact remains that pre-clinical research translated to "encouraging data" in the clinic. *Id.* Indeed, the Office Action admits that cilomast is an approved drug for the treatment of COPD. *See* Office Action, page 10. The mere assertion by the Office Action that the translation of preclinical data to clinical efficacy "can prove difficult" does not change that the fact that PDE IV inhibitors have been proven to be clinically effective in the treatment of a number of inflammatory and/or immunoregulatory conditions. Thus, far from undermining the enablement of the instant claims, Dastidar provides yet another example, in addition to those of Bielekova and Burnouf, that supports the proposition that PDE IV inhibition leads to positive clinical results in humans.

In sum, claims 5 and 8 are enabled by the instant specification in view numerous examples of compounds of the instant claims having PDE IV inhibitory activity, and the state of the art linking PDE IV inhibition with real clinical effect in man, as exemplified by Bielekova, Burnouf and Dastidar. Further, as will be discussed below, the legal standard for the enablement requirement requires far less of a showing.

C. The legal standard for enablement post-*Brana*

Clinical success in humans is not required in order to support the enablement of the instant claims, and it is legally incorrect for the Patent Office to require such proof. This issue was addressed at length in Applicants' Appeal Brief dated February 4, 2009, but it is not addressed in the instant Office Action. As was established in *In re Brana*, the mere teaching of some skepticism in the art about the predictive nature of an *in vitro* or *in vivo* model for human therapy does not render claims to a method of treatment lacking enablement. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). At issue in *Brana* was a prior art reference which taught that some laboratory oncologists were skeptical about the predictive value of certain murine tumor models provided by the applicants for human therapy. *Id.* Regardless of this fact, the Court concluded that the claims at issue were enabled because the "usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." *Brana*, 51 F.3d at 1568 (emphasis added). This is precisely what the Office Action has put in issue by questioning the connection between PDE IV inhibition and clinical efficacy in the treatment of inflammatory and immunoregulatory disease. *See* Office Action, pages 7-10.

Applicants respectfully point out that the *Brana* Court held that "the therapeutic predictive value of [the tests provided by the applicants]" are relevant in assessing the enablement requirement "only if applicants must prove the ultimate value in humans of their asserted utility,"—no such requirement exists for patentability, including the enablement requirement. *Id.* at 1566 (emphasis added). As discussed above, the teachings of Bielekova, Burnouf and Dastidar do not go as far as the reference at issue in *Brana* did, because Bielekova, Burnouf and Dastidar, read together as a whole, teach the usefulness of PDE IV inhibitors as potential therapeutic agents for the treatment of inflammatory and immunoregulator diseases and disorders.

Even assuming, *arguendo*, that the Office Action's conclusions about the allegedly skeptical nature of the teachings of Bielekova, Burnouf and Dastidar are true, the instant claims satisfy the enablement requirement because *Brana* holds that mere skepticism in a prior art reference is not enough to rebut the legal presumption of enablement. As the Court noted in *Brana,* "[t]he stage at which an invention in [the pharmaceutical] field becomes useful is well before it is ready to be administered to humans." *Id.* at 1568 (emphasis added). Thus, Applicants respectfully submit that the Office Action's rejection based on the alleged a lack of correlation between *in vitro* studies showing PDE IV inhibitory effects and clinical efficacy cannot stand in view of the legal principles set forth in *Brana* above. Indeed, adopting the Examiner's rationale, no claims to method of human treatment can be issued based on *in vitro* data, and such a result would be flatly contrary to *Brana* court's reasoning that "[t]he stage at which an invention in [the pharmaceutical] field becomes useful is well before it is ready to be administered to humans." *Brana*, 51 F.3d at 1568.

Consequently, Applicants respectfully submit that the legal principles set forth in *Brana* are entirely applicable to this application, and thus, the alleged "reason to doubt" provided by the Examiner is legally improper.

II. Conclusion

Applicants respectfully submit that all of the pending claims are allowable, and thus, respectfully request that all of the rejections be withdrawn.

The fee for an Extension of Time for two months will be paid via EFS Web. If any other fees are required, the Director is authorized to charge such fees to Jones Day Deposit Account No. 503013 (referencing 501872-999204).

Respectfully submitted,

Date: October 9, 2009

Mark D. Kafka Reg. No. 59,569
For: Anthony M. Insogna Reg. No.:35,203

JONES DAY
12265 El Camino Real, Suite 200
San Diego, CA 92130
(858) 314-1200